Statistical Information for In Vitro Bioequivalence Data

In reference to the *Federal Register* notice on the draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action: Availability*," vol. 64, No. 121, June 24, 1999, the Food and Drug Administration is providing a method for determining an upper 95% confidence limit for in vitro BE data based on nonprofile analyses using parallel designs. The method is referred to in the Statistical Analyses Section IX(B)(2)(b) of the draft guidance, and is provided in the following document, entitled In Vitro Nonprofile Bioequivalence Data: Population Bioequivalence - Parallel Designs; Method for Statistical Test of Population Bioequivalence Criterion.

BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR NASAL AEROSOLS AND NASAL SPRAYS FOR LOCAL ACTION

IN VITRO NONPROFILE BIOEQUIVALENCE DATA: POPULATION BIOEQUIVALENCE - PARALLEL DESIGNS

Method for Statistical Test of Population Bioequivalence Criterion

Since three batches are not sufficient to reliably estimate the between batch component of variance, the total variances are estimated as the between canister variance of the "super-batch" consisting of the three batches combined. In addition, this initial implementation does not include the estimation of within canister (between life stage) component of variance.

Criterion:

$$((\mu_T - \mu_R)^2 + \sigma_T^2 - \sigma_R^2) / \sigma_R^2 \leq \theta_p$$

Following the method developed by Hyslop, Hsuan, and Holder (1999) for the individual bioequivalence criterion, we propose the following method for testing this criterion. The procedure involves the computation of a test statistic which is either positive (does not conclude population bioequivalence) or negative (concludes population bioequivalence). This method is based on the work of Howe (1974) and Ting et al. (1990). The method outlined below assumes equal numbers of canisters per batch, and that three batches for each product will be combined as one "super-batch" for each product for analysis.

Notation:

n_T, n_R:	Number of canisters per batch, for T and R products
ℓ_T, ℓ_R:	Number of batches of T and R products
$\Delta = \mu_T - \mu_R$:	Mean difference of T and R products
σ_T^2, σ_R^2:	Total variance of T and R products
σ_{T0}, θ_p:	Regulatory constants

Linearized Criteria:

$$\eta_1 = (\mu_T - \mu_R)^2 + (\sigma_T{}^2 - \sigma_R{}^2) - \theta_P \cdot \sigma_R^2 < 0, \quad \text{for } \sigma_R > \sigma_{T0}$$

$$\eta_2 = (\mu_T - \mu_R)^2 + (\sigma_T{}^2 - \sigma_R{}^2) - \theta_P \cdot \sigma_{T0}^2 < 0, \quad \text{for } \sigma_R \le \sigma_{T0}$$

Estimating the Linearized Criteria:

Begin by computing the separate means and variances for the log of the measure of each product. Since three batches is not sufficient to reliably estimate the between batch component, the total variances are estimated as the between canister variance of the "super-batch" consisting of the three batches combined. Compute the total sum of squares for each product and denote them as SST_T and SST_R. Compute: $MST_T = SST_T / (n_T \cdot \ell_T - 1)$ and $MST_R = SST_R / (n_R \cdot \ell_R - 1)$ (Searle). Estimate the overall means of each product and compute:

$$\hat{\Delta} = \overline{X}_T - \overline{X}_R = \hat{\mu_T - \mu_R}.$$

$$\hat{\eta_1} = (\overline{X}_T - \overline{X}_R)^2 + MST_T - \left(1 + \theta_p\right) MST_R$$

$$\hat{\eta_2} = (\overline{X}_T - \overline{X}_R)^2 + MST_T - MST_R - \theta_p \sigma_{T0}{}^2$$

To test for population bioequivalence, compute the 95% upper confidence bound of either the reference-scaled or constant-scaled linearized criterion. The procedure for computing this is described in the next paragraphs. If this upper bound is negative, conclude population bioequivalence. If the upper bound is positive, do not conclude population bioequivalence.

95% Upper Confidence Bounds of Components:

Use the estimated total variance for T and for R based on l_T*n_T-1 and l_R*n_R-1 degrees of freedom where n_T and n_R are the number of canisters in each of the T and R batches and l_T, l_R are the number of batches of each product.

Using methods developed by Lee and Gurland for the Behrens-Fisher problem and the estimation method provided by Lee and Fineberg, compute two-sided confidence interval for $\hat{\Delta}$ based on the total variances.

Let $E0 = (\overline{X}_T - \overline{X}_R)^2$, $H0 = \max\left\{LCL^2, UCL^2\right\}$ using the two-sided interval obtained for $\hat{\Delta} = \overline{X}_T - \overline{X}_R$ which is described above (Hsu et al, 1994).

Let $E1 = MST_T$, compute $H1 = \dfrac{(\ell_T n_T - 1)E1}{\chi^2_{\ell_T n_T - 1, \alpha}}$

Let E2rs= $-\left(1+\theta_p\right) MST_R$, compute $H2rs = \dfrac{(\ell_R n_R - 1)E2rs}{\chi^2_{\ell_R n_R - 1, 1-\alpha}}$

Let E2cs= $- MST_R$, compute $H2cs = \dfrac{(\ell_R n_R - 1)E2cs}{\chi^2_{\ell_R n_R - 1, 1-\alpha}}$

For each component above, also compute $Ui = \left(Hi - Ei\right)^2$.

95% Upper Confidence Bounds for Linearized Criteria:

$$H_{\eta_1} = (E0 + E1 + E2rs) + (U0 + U1 + U2rs)^{1/2}$$

$$H_{\eta_2} = (E0 + E1 + E2cs - \theta_p {\sigma_{T0}}^2) + (U0 + U1 + U2cs)^{1/2}$$

References

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